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Stereoselective Peterson Olefinations from Bench-Stable Reagents and N-Phenyl Imines

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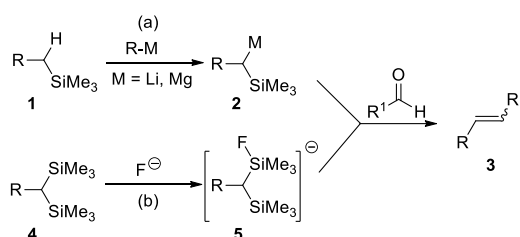
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Abstract: The synthesis of bench stable α,α -bis(trimethylsilyl)toluenes and tris(trimethylsilyl)methane is described and their use in stereoselective Peterson olefinations has been achieved with a wide substrate scope. Product stereoselectivity was poor with carbonyl electrophiles (*E/Z*-1:1 to 4:1) though this was significantly improved by employing the corresponding substituted *N*-benzylideneaniline (up to 99:1) as an alternative electrophile. Identification of the reaction by-product as *N,N*-bis(trimethylsilyl)aniline, which could be readily separated from product by aqueous acid extraction, suggests phenyl(trimethylsilyl)amide as the olefin forming leaving group and that an autocatalytic cycle was possible. This mechanistic insight prompted the development of KHMDS as a new non-fluoride activator for α,α -olefination reactions under routine conditions.

In the synthetic olefination toolbox the Peterson olefination, in spite of its great value, remains one of the lesser utilized methods for the conversion of carbonyls to alkenes.¹ The transformation is considered as a silicon analogue of the Wittig reaction with the reaction of α -silyl carbanions **2** (typically generated by deprotonation of **1** using strong lithium or magnesium bases) with carbonyls providing the alkene product **3** and trimethylsilyl oxide by-product (Scheme 1, route (a)).² Intermediate β -hydroxysilanes can be isolated when the silyl carbanion used is not stabilized (e.g. R = alkyl), which upon treatment with either base or acid can deliver the corresponding (*E*)- or (*Z*)-alkene stereoselectively.³ For stabilized α -silyl carbanions (e.g. R = Ar) these intermediates are not isolated and stereo-control has yet to be achieved.⁴ A further disincentive to the use of the reaction is that the generation of the silyl anions **2** are substrate dependent and can often require non-trivial conditions.

Yet, if solutions to these issues were in hand, an inherent advantage of the Peterson olefination is its superior atom-economy over the Wittig reaction as it produces low molecular silicon by-product in the carbon-carbon double bond forming step rather than crystalline triphenylphosphine oxide.⁵ An alternative approach to the generation of the α -silyl carbanions that does not require strong organometallic bases, is to use geminal bis-trimethyl silanes **4** as starting substrates and a fluoride source to promote generation of the α -silyl carbanion precursor **5** (Scheme 1, route (b)). In spite of the fact that the bis silanes **4** are bench-stable (analogous to the Wittig phosphonium salt), this approach has received very limited practical use, perhaps due to the lack of general routes for their synthesis.^{4e-g,6}

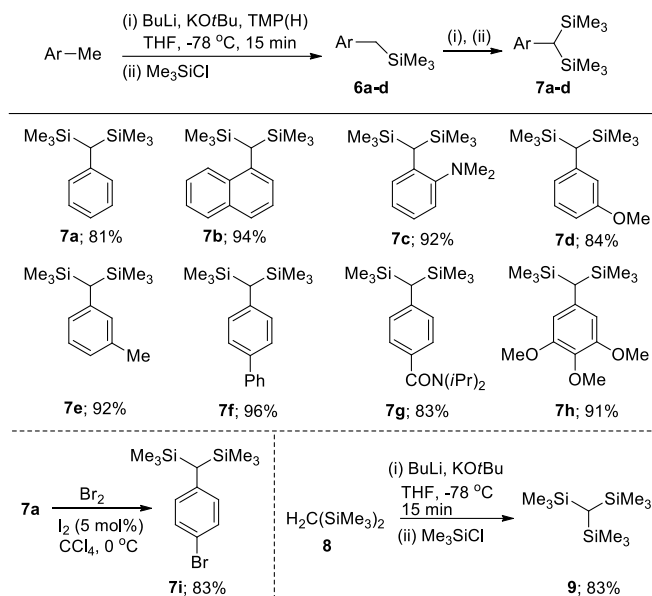


Scheme 1. Peterson olefination.

In this report we illustrate a new general two step approach for the synthesis of α,α -bis(trimethylsilyl)toluenes **7a-h** from their corresponding toluenes using identical synthetic conditions for both steps. We have developed a routine rt method for their use in olefination reactions and shown, for the first time, how the stereocontrol can be achieved by the use of aniline derived *N*-aryl imine electrophiles. In addition this method is extended to the complementary tris-trimethylsilane **9** which opens a new route to vinyl trimethylsilanes, which are in themselves important substrates for cross-coupling transformations in alkene synthesis.⁷

Synthesis of (arylmethylene)bis(trimethylsilanes) **7a-h** was achieved by the regioselective benzylic metalation of the parent toluene using BuLi, KO^tBu, TMP(H) in THF (LiNK conditions)⁸ and TMSCl quench to form the substituted benzylsilanes **6a-h** with a repeat of these conditions providing the desired olefination reagents (Scheme 2, top panel). Introduction of a sensitive bromine functional group, that would not be tolerant of the chemistry required for the geminal bis-silane synthesis, was achieved from **7a** giving with *p*-bromo derivative **7i** obtained in an excellent 83% yield (Scheme 2, left bottom panel). Tris(trimethylsilyl)methane **9** was generated by deprotonation of bis(trimethylsilyl)methane **8** and TMSCl quench (Scheme 2, right bottom panel).

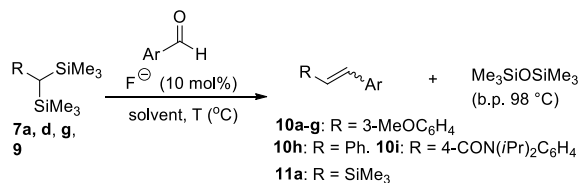
With the olefination reagents in hand their use in fluoride promoted reaction with aldehydes was explored to identify mild activation conditions and record the effects of substituents on product *E/Z* selectivity (Table 1). It was found that reaction of **7d** with benzaldehyde proceeded smoothly in either THF or DMF using TBAF, TBAT or CsF respectively, giving the stilbene product in each case but with virtually no stereoselectivity (Table 1, entries 1-3).



Scheme 2. Synthesis of (arylmethylene)bis(trimethylsilanes) **7a-i** and tris(trimethylsilyl)methane **9**.

Reaction with other aldehydes showed no significant change in product *E/Z* ratio which is consistent with previous reports (entries 4-9).⁴ Similar results were obtained with **7a** using TBAF as activator (entry 10). Only derivative **7g** containing an electron withdrawing group and the tris(trimethylsilyl)methane **9** showed moderate 80/20 *E/Z* at selectivity (entries 10-13).⁹ While the lack of stereo-control is a major drawback, monitoring of the reaction by ¹H NMR in THF-*d*₈ revealed that hexamethyldisiloxane was the reaction byproduct, which as a low boiling solvent (98 °C) can be readily removed (SI).

Table 1: Screening of olefination reaction conditions with carbonyls.



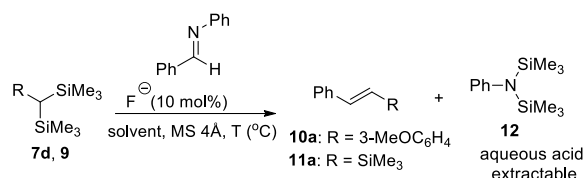
entry	7/9	solvent	Ar	T (°C)	yield (%)	<i>E/Z</i> ^a
1	7d	THF	Ph	rt ^b	10a /56	56/44
2	7d	THF	Ph	70 ^b	10a /77	54/46
3	7d	DMF	Ph	80 ^e	10a /82	51/49
4	7d	THF	4-BrC ₆ H ₄	70 ^b	10b /74	52/48
5	7d	THF	4-MeOC ₆ H ₄	70 ^b	10c /77	52/48
6	7d	THF	4-MeC ₆ H ₄	70 ^b	10d /64	53/47
7	7d	THF	2-naphthyl	70 ^b	10e /73	47/53
8	7d	THF	(<i>E</i>)-PhCH=CH	70 ^b	10f /89	50/50
9	7d	THF	4-CNC ₆ H ₄	70 ^b	10g /70	51/49

10	7a	THF	4-MeOC ₆ H ₄	rt ^d	10h / 70	53/47
11	7g	THF	4-MeOC ₆ H ₄	rt ^b	10i / 64	80/20
12	9	THF	Ph	70 ^f	11a /85	80/20
13	9	THF	Ph	rt ^g	11a /65	75/25

^a*E/Z* ratio determined by ¹H NMR of crude extracted product. Fluoride source ^bTBAT, ^cCsF, ^dTBAF. ^e1equivCsF used. ^f20 mol% TBAT used. ^g20 mol% TBAF used.

As neither substrate nor reaction conditions had any significant general influence on the stereochemical outcome of the reaction, a new approach was sought to do so. Computational studies on the Peterson olefination mechanism have described that, in the absence of a coordinating counterion, the addition step was rate limiting and as such it should be sensitive to steric and electronic influences.¹⁰ In an effort to exert such influences in a general manner, (*E*)-*N*-benzylideneanilines were chosen as alternative electrophiles to aldehydes which could be readily generated via their condensation with inexpensive aniline (Table 2).¹¹ Gratifyingly, the reaction of **7d** in either THF with TBAT at reflux or DMF / CsF at rt gave the product **10a** in modest yield but with dramatically improved *E/Z* selectivity of 94/6 (Table 2, entries 1,2). The product yield was found to improve to 77% when the reaction was carried out in DMF at 80 °C using 30 mol% CsF (entry 3). Applying similar conditions (except elevating the amount of CsF to 1 equiv), the tris(trimethylsilyl)methane **9** gave **11a** in a 83% yield and *E/Z* ratio of 99:1 (entry 4). Following the reaction course of **7d** with *N*-benzylideneaniline in DMF-d₇ showed that

Table 2: Optimization of olefination conditions with imine electrophiles.

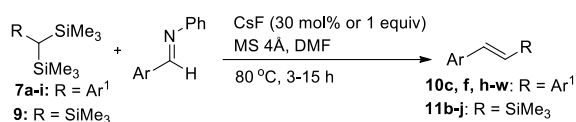


entry	7d/9	fluoride	solvent	T (°C)	yield (%)	<i>E/Z</i> ^a
1	7d	TBAT	THF	70	10a /15	94/6
2	7d	CsF ^b	DMF	rt ^c	10a /59	97/3
3	7d	CsF ^c	DMF	80	10a /77	96/4
4	9	CsF ^b	DMF	80	11a /83	99/1

^a*E/Z* ratio determined by ¹H NMR of crude extracted product. ^b1 equiv CsF used. ^c30 mol% CsF used.

1,1,1-trimethyl-*N*-phenyl-*N*-(trimethylsilyl)silanamine **12** was produced as by-product during the course of the reaction (SI). Compound **12** was readily separable from alkene product by aqueous acid extraction during which it was seen to desilylate and generate aniline.

Table 3: Stereochemistry control in Peterson olefination with imine electrophiles.

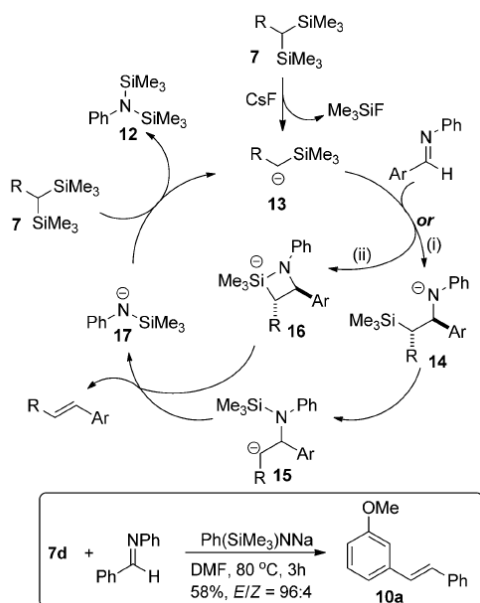


entry	7 / 9	Ar	prod	yield (%)	<i>E/Z</i> ^a
1	7a	Ph	10j	79	92/8
2	7a	4-MeOC ₆ H ₄	10h	60	91/9
3	7b	2-ClC ₆ H ₄	10k	83	98/2
4	7b	ferrocenyl	10l	82	99/1
5	7c	2-ClC ₆ H ₄	10m	71	98/2
6	7d	4-MeOC ₆ H ₄	10c	62	92/8

7	7d	(<i>E</i>)-PhCH=CH	10f	71	91/9
8	7e	2-naphthyl	10n	53	99/1
9	7e	4-FC ₆ H ₄	10o	73	95/5
10	7f	3-MeOC ₆ H ₄	10p	89	99/1
11	7f	ferrocenyl	10q	41	99/1
12	7g	Ph	10r	77	99/1
13	7g	4-FC ₆ H ₄	10s	69	99/1
14	7h	4-BrC ₆ H ₄	10t	68	99/1
15	7h	4-MeOC ₆ H ₄	10u	83	99/1
16	7i	4-FC ₆ H ₄	10v	87	99/1
17	7i	2-MeOC ₆ H ₄	10w	11	99/1
18	9	2-ClC ₆ H ₄	11c	71	97/3
19	9	3-MeOC ₆ H ₄	11d	73	99/1
20	9	4-BrC ₆ H ₄	11e	51	99/1
21	9	4-FC ₆ H ₄	11f	56	99/1
22	9	4-MeOC ₆ H ₄	11b	61	99/1
23	9	4-Me ₂ NC ₆ H ₄	11g	60	99/1
24	9	4-MeOC(O)C ₆ H ₄	11h	44	99/1
25	9	2-naphthyl	11i	70	99/1
26	9	ferrocenyl	11j	47	97/3

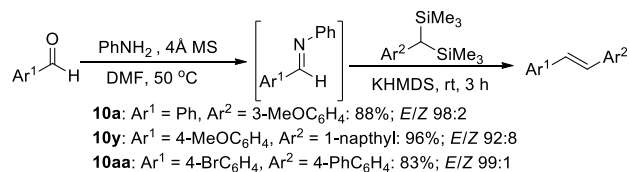
^a*E/Z* ratio determined by ¹H NMR of crude extracted product.

The generality of *E*-product selectivity was investigated using ten different olefination reagents **7a–i** and **9**, with thirteen different *N*-phenyl imines chosen to reflect differing electronic and steric factors (Table 3). Remarkably, the excellent *E* selectivity was observed in all reactions with the stilbene products **10** obtained in *E/Z* ratios ranging from 91:9 to 99:1 (Table 3, entries 1–17) and substituted trimethyl(styryl)silanes **11** ranging from 97:3 to 99:1 (entries 18–26). While further investigation is required to fully explain the *N*-phenyl imine stereocontrol two influential differences between the imine and carbonyl reaction pathways would be the increased sterics involved in the addition of **13** and the effect of the phenyl(trimethylsilyl)amide leaving group **17**. Loss of **17** could be envisaged 1) following the formation of the carbanion **15** by an 1,3-aza-Brook-type rearrangement of **14** or 2) following the concerted formation of the substituted 1-aza-2-silacyclobutane **16** (Scheme 3).[12] Completion of the reaction cycle with the formation of **12** as a byproduct indicates the possibility of an autocatalytic cycle in which **17** reacts with starting material **7** to generate **12** and **13** (Scheme 3).[13] This was confirmed by the reaction of **7d** with *N*-benzylideneaniline by using one equivalent of **17** (generated by the reaction of 1,1,1-trimethyl-*N*-phenylsilanamine with NaH) to promote the reaction. The expected stilbene product **10a** was obtained with an identical *E/Z* selectivity as observed with the CsF-promoted reaction (Scheme 3, inset). This we believe is the first demonstration of an autocatalytic Peterson reaction.



Scheme 3. Mechanistic cycle.

While the synthesis of *N*-benzylideneanilines could be considered trivial it does add an additional synthetic step to the overall process. As such, a one-pot method was developed which first conducted the aldehyde/aniline condensation in DMF following which the bis(silane) reagent was added and olefination performed in situ. Using **7b**, **d**, and **f** as representative bis(silanes), this approach worked well with the stilbenes **10a**, **10x,y** isolated in comparable yield and *E*-selectivity as the approach outlined above (Scheme 4).



Scheme 4. One-pot (*E*)-selective synthesis of stilbenes

In summary, a new general two-step synthesis of α,α -bis(trimethylsilyl) toluenes and tris(trimethylsilyl)methane has been developed providing access to bench-stable Peterson olefination reagents. Poor *E/Z* selectivity was obtained in their reaction with aldehydes but when the corresponding substituted *N*-benzylideneanilines were employed as electrophiles high *E* selectivity was observed for a wide range of substrates. Identification of the reaction byproduct as aqueous extractable *N,N*-bis(trimethylsilyl)aniline maintains the advantage of Peterson olefinations in generating a readily removable byproduct. Evidence for an autocatalytic cycle has been established with the olefin forming leaving group being capable of propagating the reaction. As the use of imine electrophiles for aza-Peterson olefinations has not been previously studied, the scope of this approach is currently being further explored in conjunction with additional mechanistic investigations.

Experimental Section

General procedure for the olefination of (benzyl)bis(trimethylsilane) with *N*-phenyl imines

A solution of (benzyl)bis(trimethylsilane) (0.48 mmol) and substituted *N*-benzylideneaniline (0.40 mmol) in anhydrous DMF (2.0 mL) with 4 Å molecular sieves was treated with CsF (0.12 mmol) under N₂ and the resulting solution was heated at 80

°C until the reaction reached completion. The reaction mixture was quenched with water. The residue was extracted with diethyl ether (20 mL x 3). Organic layers were combined and washed with water and brine, dried over anhydrous sodium sulfate, and concentrated. Purification by silica gel chromatography eluting with petroleum ether/ethyl acetate gave the corresponding alkene. The *E/Z* ratios for the alkene products were determined by ¹H NMR spectroscopic analysis.

Acknowledgements

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Keywords: bench-stable reagents · imines · organic synthesis · Peterson olefination · stereoselectivity

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